

Interventions for the treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis

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The research evidence on the effectiveness of interventions for the treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) published in a recent issue of *Effective Health Care* is reviewed.

This article summarises the research evidence presented in a recent issue of *Effective Health Care* on interventions for the treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).¹ It provides an overview of the evidence from a systematic review of randomised controlled trials commissioned by the Department of Health.² The results of the systematic review were found to be similar to those of another systematic review carried out in the USA at the same time,³ and the two have been combined and published together in 2001.⁴

BACKGROUND

Chronic fatigue syndrome (CFS) consists of a range of symptoms including fatigue, headaches, sleep disturbances, difficulties with concentration, and muscle pain. The defining characteristic has been reported to be debilitating fatigue.⁵⁻⁷ Children and adults present with similar symptoms.⁸ Myalgic encephalomyelitis (ME) is sometimes reported to be a separate syndrome from CFS, characterised by muscle weakness, pain and neurological disturbance.⁹ It has been suggested that CFS and ME are part of a group of similar symptom complexes such as postviral fatigue syndrome, fibromyalgia and neurasthenia.⁶ ME is sometimes diagnosed in people with these symptom complexes in the UK, but is not commonly diagnosed in other countries such as the USA.¹⁰ In this review the condition will be referred to as CFS/ME.

The cause of CFS/ME remains unknown, although various hypotheses have been suggested that include one or more of the following factors: immunological, viral, psychological and neuroendocrine. Diagnosis is based entirely on symptoms reported by the patient. Definitions commonly used tend to be research criteria.¹¹ Two frequently used definitions for CFS are the UK (Oxford) criteria⁵ and the US Centers for Disease Control and Prevention criteria.⁶ Both state that debilitating fatigue must be present for at least 6 months, that there is some functional impairment, and that these have not been caused by any other identifiable clinical condition. The definitions differ, however, in the number and severity of other symptoms that must be present. In practice a

clinical assessment is used which aims to increase the probability of a correct diagnosis of CFS/ME and to rule out other conditions.¹¹ This involves taking a full clinical history, a mental health evaluation, sleep evaluation, and a physical examination. It is recommended that a series of basic screening tests be undertaken to exclude other conditions that can present as fatigue.¹¹

Estimates of prevalence vary, and may be attributed to the diversity in diagnostic criteria and to variations in the extent to which alternative medical and psychiatric diagnoses have been excluded. One small UK study reported that the point prevalence of CFS was 0.6% (95% confidence interval 0.2 to 1.5) using the UK (Oxford) criteria.¹² A larger UK study reported a prevalence ranging from 0.5%, when comorbid psychological disorders were excluded, to 2.6% when they were not.¹³ Onset is most commonly reported to be from the early twenties to mid-forties. It is reported to be approximately twice as common in women as in men, affects all social classes to a similar extent, and affects all ethnic groups.¹¹ Based on an estimate of adult population prevalence of 0.4%, the CFS/ME Working Group reported that a general practice with a population of 10 000 patients is likely to have 30-40 patients with CFS/ME, about half of whom may need input from specialist services.¹¹

It is generally recognised that prognosis is variable. Many patients improve quite quickly. However, in those who do not improve quickly, the illness can persist for a long time. The prognosis tends to be worse for severely ill patients than for less severely ill patients.¹¹ The findings from prospective natural history studies are varied.³ At 12-18 months, rates of self-reported global improvement in symptoms range from 11% to 64% and rates of self-reported worsening of symptoms from 15% to 20%.

CURRENT SERVICE PROVISION

The recent CFS/ME Working Group Report¹¹ stated that the provision of services specifically designed for patients with CFS/ME is limited in some areas and non-existent in others. While patients have access to the normal range of primary, secondary and tertiary care services, few are tailored to this patient group. Specialist services for children and young people, including inpatient facilities, are limited to a few nationwide. Referrals from primary care are to one or more specialists such as general physicians, immunologists, neurologists, haematologists, and psychiatrists. The CFS/ME Working Group Report suggests that the lack of locally based specialist services may be a problem for patients who need

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Table 1 Summary of study results

Treatment	Duration of follow up† (weeks)	Number of participants	Outcomes investigated	Any effect	Overall effect
Behavioural					
GET ²⁶	12	66	PH; PS; LAB; QOL	+	+
GET ²⁷	52 (26)	148	PH; PS; QOL	+	+
GET & fluoxetine ²⁸	26	136	PH; PS; QOL	+	<>
CBT ²⁰	26 (and 5 years)	60	PH; PS; QOL	+	+
CBT ²¹	61 (35)	270	PH; PS; QOL	+	+
CBT ¹⁹	52	60	PH; PS; QOL	+	+
CBT + DLE ²²	30 (16)	90	PH; PS; LAB; QOL	+	<>
Immunological					
Immunoglobulin ³¹	26 (13)	71	PH	+	+
Immunoglobulin ³⁰	21	30	PH; LAB; QOL	+	<>
Immunoglobulin ²⁹	26 (13)	49	PS; QOL	+	<>
Immunoglobulin ³³	26 (13)	99	PH; PS; LAB; QOL	<>	<>
Gammaglobulin ³²	17	19	QOL	+	+
Ampligen ³⁴	26	92	RU; PH; PS	+	+
Terfenadine ³⁵	9	30	PH; QOL	<>	<>
Antiviral					
Alpha interferon ³⁷	12	30	LAB; QOL	+	<>
Interferon ³⁶	52 (12)	20	PH	+	+
Aciclovir ³⁸	18 (13)	27	PH; PS; LAB; QOL	-	<>
Ganciclovir ³⁹	26	11	QOL	<>	<>
Pharmacological					
Hydrocortisone ⁴³	9	32	PH; QOL	+	<>
Hydrocortisone ⁴⁴	12	70	PH; PS; QOL	+	<>
Fludrocortisone ⁴⁶	11 (9)	100	PH; PS; LAB; QOL	<>	<>
Fludrocortisone ⁴⁵	18	25	PH; PS; QOL	<>	<>
Fluoxetine ⁴¹	12 (8)	107	PH; PS; QOL	<>	<>
Phenelzine ⁴⁰	6	24	PH; PS; QOL	<>	<>
Moclobemide ⁴²	6	90	PH; PS; LAB; QOL	<>	<>
Sulbutiamine ⁴⁸	4	326	PH; QOL	<>	<>
Galanthamine hydrobromide ⁴⁷	2	49	PH; PS; QOL	<>	<>
Oral NADH ⁵⁰	12	26	QOL	+	+
Growth hormone ⁴⁹	12	20	PH	<>	<>
Supplements					
Essential fatty acids* ⁵²	13	63	LAB; QOL	+	+
Essential fatty acids* ⁵¹	13	50	PS; QOL	+	<>
Magnesium ⁵³	6	34	PH; PS; LAB; QOL	+	+
Liver extract ⁵⁴	2	15	PH; PS; QOL	<>	<>
General supplements ⁵⁵	7	12	PH	+	+
Complementary/alternative					
Any homoeopathic remedy ⁵⁸	26	104	PH; PS	+	<>
Any homoeopathic remedy ⁵⁷	52	64	QOL	+	+
Massage therapy ⁵⁶	5	20	PH; PS; LAB	+	+
Multi-treatment					
Multi-treatment ⁵⁹	13	72	PH; QOL	+	+

+ = a positive effect of treatment; - = a negative effect of treatment; <> indicates no effect of treatment; GET = graded exercise therapy; CBT = cognitive behavioural therapy; DLE = dialysable leukocyte extract.

*Essential fatty acids (both studies) = 36 mg gamma-linoleic acid (GLA), 17 mg eicosapentanoic acid (EPA), 11 mg docosahexanoic acid (DHA), 255 mg linoleic acid (LA), plus 10 IU vitamin E.

†For studies in which the duration of intervention was different from the duration of follow up, the duration of intervention is shown in brackets.

Outcome codes: RU = resource use; PH = physical; PS = psychological; LAB = laboratory and physiological; QOL = quality of life and general health.

Outcomes which showed a significant difference between intervention and control groups are highlighted in bold.

access to services but are unable to reach them, and for commissioners who wish to reduce the cost of out of area treatments.

TREATMENT AND MANAGEMENT

A number of interventions have been used in the treatment and management of CFS/ME. The CFS/ME Working Group Report² identified three therapeutic strategies as potentially beneficial: cognitive behavioural therapy (CBT), graded exercise therapy (GET), and pacing.

The evidence for CBT and GET comes from randomised controlled trials while that for pacing comes from patient reports and clinical experience. The report called for more research, particularly into pacing. The Department of Health has now asked the Medical Research Council to develop a broad strategy for advancing biomedical and health services research on CFS/ME (<http://www.doh.gov.uk/cmo/CFS/MEemereport/response.htm>).

An overview of the included studies and main findings from the systematic review is presented in table 1. To provide an

overall estimate of whether each study found a positive, negative or no effect of the intervention, all studies were classified according to two separate methods: whether the study showed any effect of the intervention and whether it showed any overall effect.

Interpreting the findings

Some of the interventions have been evaluated in only one or two studies, which may limit the generalisability of the findings. Many studies had relatively small sample sizes, did not use standardised outcome measures, and failed to use an intention-to-treat analysis. Many of the data presented in the studies were limited and, because of differences between studies (for example, outcomes reported, types of data presented and interventions evaluated), it was not possible to calculate pooled summary statistics. Also of importance are the inclusion criteria specified in some trials, such as participants being eligible if they could physically get to the clinic. Those people who were unable to walk or to get out of bed were excluded and so it has not been possible to assess

whether the interventions investigated would be effective, ineffective, or even hazardous for a more severely disabled group of people. Uncontrolled studies of interventions for severely disabled people with CFS/ME are reported to have shown no evidence of harm.^{14–16} However, these studies do not form part of the evidence base for this review.

In some of the trials, limited information was provided for patients who were ineligible or about the baseline functioning of many of those who were included. It is therefore difficult to extrapolate the findings to other people with CFS/ME. In those trials that did report baseline functioning, the majority of participants were unable to take part in full time employment. Another limitation of most of the trials was the duration of follow up. The relapsing nature of the condition suggests that follow up should continue for an additional 6–12 months (at least) after the intervention period has ended to confirm whether any improvement persists for a relevant period of time.

Many different outcomes were reported and were measured using a variety of scales. Outcomes such as “improvement”, where participants were asked to rate themselves as better or worse after the intervention, were frequently reported. However, the person may feel better able to cope with daily activities because they have reduced their expectations of what they should achieve, rather than because they have made any recovery as a result of the intervention. A more objective measure of the effect of any intervention would be whether participants had increased their working hours, returned to work, or increased their physical activities, and these outcomes were evaluated in some studies.

Some interventions have been evaluated using non-randomised controlled trials, including osteopathy, modified CBT (based on coping within limits set by symptoms), and other multi-treatment approaches. These have been reviewed elsewhere and have yet to be evaluated in randomised controlled trials.^{2–4} Randomised controlled trials are also needed to evaluate the effectiveness of pacing. Pacing is an energy management strategy in which patients are encouraged to achieve an appropriate balance between rest and activity. This usually involves living within physical and mental limitations imposed by the illness, and avoiding activities to a degree that exacerbates symptoms or interspersing activity with periods of rest.¹¹ An understanding of the underlying mechanisms of CFS/ME is likely to aid in the development of effective treatment or management programmes.

Behavioural interventions

Recommendations about the use of behavioural interventions such as CBT can be misinterpreted when the perceived suggestion is that CFS/ME is a psychological condition. However, conclusions about the cause of the condition cannot be drawn from the fact that certain treatments may be effective. Behavioural interventions, and CBT in particular, have been used effectively in other physical illnesses such as heart disease¹⁷ and chronic low back pain.¹⁸

Four randomised controlled trials evaluated weekly or biweekly sessions of CBT. CBT was compared with routine medical care in one trial ($n=60$),¹⁹ with relaxation in a second trial ($n=60$),²⁰ and with natural course (control) in a third ($n=270$).²¹ The fourth trial ($n=90$) compared four groups: CBT plus placebo injections; CBT plus leukocyte extract (a fraction of blood containing white blood cells); a control clinic plus leukocyte extract; and a control clinic plus placebo injections.²²

Participants who received combined leukocyte extract and CBT showed a beneficial effect on general health compared with the other three groups.²² The remaining three trials reported a beneficial effect of CBT when compared with control groups.^{19–21} Two randomised controlled trials found a significant global improvement at follow up.^{19–20} All but the

combined leukocyte extract/CBT study also found significant improvements in physical functioning and fatigue. Neither of the two studies that assessed depression found any differences between groups.^{19–20} One of these trials also followed patients for 5 years after the intervention^{20–23} and found that global improvement was greater in the intervention group, as was the mean number of hours worked per week and the proportion of participants who completely recovered (the definition of “completely recovered” was based on fatigue and physical functioning scores as well as UK (Oxford) CFS criteria).²³ However, no significant differences were reported between the groups for individual outcomes of physical functioning, fatigue, general health, symptoms, relapses, or the proportion of participants that no longer met the UK (Oxford) criteria for CFS.

Two randomised controlled trials of CBT in primary care are reported to be ongoing.^{24–25}

The studies evaluating CBT reported no adverse effects of the intervention except in one trial two participants dropped out of the CBT group because they felt that a deterioration in their symptoms was due to the intervention.¹⁹ A second randomised controlled trial reported dropout rates of 20–35% in all three intervention groups, with the highest rates in the CBT group, but the reasons for the dropouts were not reported.²¹

The effects of GET were investigated in three randomised controlled trials ($n=66$, $n=148$ and $n=136$), two of which found overall beneficial effects.^{26–27} The third found some beneficial effects.²⁸ When exercise was combined with fluoxetine there was no additional effect.²⁸ One trial assessed different interventions to encourage graded exercise and found benefits from GET when compared with standardised medical care for all outcomes investigated.²⁷ The studies did not report any specific adverse effects of GET although two studies did report withdrawals that may have been related to adverse effects of the intervention.

Immunological interventions

Five randomised controlled trials investigated the effects of immunoglobulin G (an antibody fraction of blood); two found some positive effect ($n=30$, $n=49$)^{29–30} and two found an overall beneficial effect ($n=19$, $n=71$).^{31–32} One was conducted in young people aged under 18.³¹ The fifth and largest ($n=99$) found no effect of treatment.³³

One randomised controlled trial evaluated ampicillin ($n=92$) and found an overall beneficial effect.³⁴ In this trial participants were grouped according to whether they had evidence of human herpes virus 6 (HHV-6) infection and no differences were found between the groups in response to ampicillin. Another trial which assessed the combined effect of leukocyte extract and CBT ($n=90$) found no effect of leukocyte extract on its own but found a beneficial effect on general health in the group receiving both leukocyte extract and CBT.²² A third trial which evaluated the antihistamine terfenadine ($n=30$) found no beneficial effects.³⁵

Some severe adverse effects were noted in participants in the immunological intervention groups. Two of 99 patients had to withdraw from immunoglobulin treatment due to severe constitutional symptom reactions.³³ One recipient also withdrew because of mild but transient liver failure,²⁹ and phlebitis has also been found with immunoglobulin infusions.²⁹ It should be noted that immunoglobulins and leukocyte extract are blood products and there are known risks associated with their use, such as the possible transfer of infectious diseases.

Antiviral interventions

Two randomised controlled trials evaluated interferon, one of which found an overall beneficial effect ($n=20$) and the other reported only within group differences and so no conclusion

can be drawn from this study.^{36, 37} The effect of aciclovir was investigated in one small trial (n=27) and a negative effect was reported for anxiety, depression and confusion with the control group showing a greater improvement in symptoms than the treatment group.³⁸ Another small randomised controlled trial investigated the effects of ganciclovir (n=11) and found no significant differences between the intervention and control groups.³⁹ Three patients had to withdraw from aciclovir treatment due to reversible renal failure.³⁸ In the ganciclovir study two of the 11 participants who were undergoing right ventricular endomyocardial biopsies experienced serious pericardial bleeding and so the study was ended prematurely.³⁹

Pharmacological interventions

Antidepressants

The effects of antidepressants were investigated in two randomised controlled trials (n=24, n=107). No benefit was found in patients with CFS/ME from treatment with antidepressants (either in treating symptoms of depression or any of the other outcome measures reported).^{40, 41} The trial of fluoxetine⁴¹ also reported no differences in response between depressed and non-depressed participants. One trial (n=90) investigated the effect of moclobemide (a monoamine oxidase inhibitor) and found no benefit of treatment.⁴² This trial also found no differences in response between those with major depression or general psychological distress and those without, or between those with reduced immune responses and those without.⁴²

Corticosteroids

The effects of steroid treatment were investigated in four randomised controlled trials.⁴³⁻⁴⁶ Two of these trials evaluated hydrocortisone (n=70, n=32) and both reported some beneficial effect.^{43, 44} The other two trials assessed fludrocortisone (n=25, n=100) and did not find any beneficial effects.^{45, 46} One trial assessed participants who had been ill for ≥ 3 years separately from those who had been ill for < 3 years. No differences in response to fludrocortisone between the two groups were reported.⁴⁶

Anticholinergic agents

Two studies evaluated anticholinergic agents (drugs which inhibit the neurotransmitter acetylcholine at neuromuscular junctions, n=49 and n=326)^{47, 48} and reported no significant effects of the intervention.

Other pharmacological agents

One study assessed the growth hormone genotropin (n=20) and found no significant effects of the intervention.⁴⁹ Oral nicotinamide adenine dinucleotide (NADH) led to a greater improvement in symptoms (the only outcome investigated) in the intervention group compared with the control group in one small randomised controlled trial (n=26).⁵⁰

Adverse events serious enough to cause withdrawal from the studies occurred with fludrocortisone,⁴⁶ moclobemide,⁴² sulbutiamine,⁴⁸ galanthamine hydrobromide,⁴⁷ phenelzine,⁴⁰ and fluoxetine.⁴¹

Supplements

Two randomised controlled trials investigated the effect of essential fatty acid supplements. One (n=50) reported some positive effects⁵¹ and another (n=63) reported an overall beneficial effect.⁵² Magnesium supplements were found to have an overall beneficial effect in one small trial (n=34).⁵³ One very small randomised controlled trial (n=15) of liver extract reported no beneficial effects.⁵⁴ Another trial (n=12) evaluated general supplements and found no effect.⁵⁵ The randomised controlled trial of magnesium supplements reported that two participants left the intervention group after experi-

encing a generalised rash.⁵³ The other studies did not report any adverse effects.

Complementary/alternative interventions

An overall beneficial effect of massage therapy was found in one small randomised controlled trial (n=20).⁵⁶ Two trials assessed the effectiveness of homoeopathy.^{57, 58} One large trial (n=104) found a positive effect (preliminary results)⁵⁸ and the second (n=64) found an overall positive effect.⁵⁷ There were no reports of adverse events in any of these studies.

Multi-treatment

An overall beneficial effect on a range of symptoms was found in a randomised controlled trial (n=72) of a symptom based multi-treatment approach in patients with CFS/ME and fibromyalgia.⁵⁹ This programme involved treating specific patient symptoms with a variety of medications. All patients in both the control and intervention groups also received nutritional supplements.

IMPLICATIONS

- A total of 38 randomised controlled trials have investigated the effectiveness of seven different categories of intervention: behavioural, immunological, antiviral, pharmacological, supplements, complementary/alternative, and multi-treatment.
- Overall, the interventions had mixed results in terms of effectiveness. All conclusions about effectiveness should be considered together with the methodological inadequacies in some of the studies.
- Interventions which have shown evidence of effectiveness include cognitive behavioural therapy and graded exercise therapy.
- There is insufficient evidence about how subgroups of patients may respond differently to treatments and further studies investigating additional subgroups are needed.
- In some of the studies bed or wheelchair restricted patients and children have been excluded, which raises questions about the applicability of findings to all people with CFS/ME.
- Immunoglobulin is the only intervention that has been investigated in young people. Two studies of CBT in children aged 10–18 are ongoing, one of which is of family focused CBT (G Bleijenberg, personal communication, 10 March 2001).⁶⁰
- There is insufficient evidence for additive or combined effects of treatments where more than one treatment is used.
- Future research could usefully compare CBT and GET. A study comparing the effects of CBT and GET is ongoing in patients with chronic fatigue (27% have a diagnosis of CFS/ME) (L Darbishire, personal communication, 17 March 2001).
- Future research needs to combine scientific rigour with patient acceptability and good quality research is needed to evaluate the effectiveness of pacing, ideally in comparison with CBT and GET. The large number of outcome measures used makes standardisation of outcomes a priority for future research.

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